REMARKS

In the instant amendment, Claim 16 has been canceled. Claims 15, 19, 22, and 23 have been amended. New Claims 30-32 have been added. Upon entry of the amendment, Claims 15, and 17-32 will be pending and under consideration.

I. THE AMENDMENT OF THE CLAIMS

Claim 15 has been amended by the insertion of the phrase, "wherein the mutant polymerase is suitable for polymerase chain reactions." The amendment to Claim 15 is supported by the specification, for example, on page 7, lines 12-15, and Claims 1 and 14 as originally filed.

Claim 19 has been amended by the insertion of, "wherein the difference between the mutant polymerase and the wild-type form consists of the single amino acid substitution of the tyrosine of the Y-GG/A amino acid motif." The amendment to Claim 19 is supported by the specification, for example, on page 3, lines 3-4.

Claim 22 has been amended to correct a typographical error.

Claim 23 has been amended to recite, "The mutant polymerase of Claim 22 wherein the tyrosine of the Y-GG/A amino acid motif is substituted with an asparagine." The amendment to Claim 23 is supported, for example, by Claim 5 as originally filed.

New Claim 30 recites, "The mutant polymerase of Claim 21 wherein the tyrosine of the Y-GG/A amino acid motif is substituted with a tryptophan or a histidine." Claim 30 is supported, for example, by Claim 3 as originally filed.

New Claim 31 recites, "The mutant polymerase of Claim 22 wherein the tyrosine of the Y-GG/A amino acid motif is substituted with a serine." Support for Claim 31 is found, for example, in Claim 5 as originally filed.

New Claim 32 recites, "A polymerase chain reaction process comprising contacting the mutant polymerase of Claim 15 with nucleotides, a primer and a polynucleotide template under conditions suitable for amplification of the polynucleotide template." Claim 32 is supported, for example, in the specification at page 3, lines 7-9, page 8, lines 11-12, page 16, lines 16-32, and Claim 14 as originally filed.

As th amendments to the claims are fully supported by the specification and claims as originally filed, they do not constitute new matter. Entry thereof is respectfully requested.

II. THE OATH/DECLARATION

The Patent Office objected to the oath or declaration as being defective for containing non-initialed and/or non-dated alterations. A new declaration and power of attorney is submitted herewith, which Applicants submit is in compliance with 37 C.F.R. 1.67(a). Accordingly, Applicants respectfully request that the objection to the oath or declaration as being defective be withdrawn.

II. CLAIM REJECTIONS

Applicants note that the only basis for rejection of any claims in the final Office Action mailed January 24, 2003, is under 35 U.S.C. § 103(a). For this reason, Applicants kindly request that the Patent Office indicate whether or not the Patent Office has withdrawn the previous rejections of Claims 26 and 27 under 35 U.S.C. § 112 as stated in the Office Action mailed June 5, 2002, and to which Applicants fully responded in the Amendment and Response mailed November 11, 2002.

III. REJECTION OF CLAIMS 15-29 UNDER 35 U.S.C. § 103

Claims 15-29 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Geneseq AAW29323 (the sequence in Frey et al., DE 196 11 759 A1) in view of Pisani *et al.* (1998), *Biochemistry* 37, 15005-12, Truniger *et al.* (1996), *EMBO J.* 15(13), 3430-41, and Truniger *et al.* (1999), *J. Mol. Biol.* 286, 57-69. The rejection of Claim 16 is moot in view of the cancellation of Claim 16. Applicants respectfully submit that the references taken either alone or in any combination do not teach or suggest each and every element of amended Claim 15, or any one of Claims 17-29 that depend from amended Claim 15. For these reasons the rejection of Claims 15-29 under 35 U.S.C. § 103(a) should be withdrawn.

The legal standard of *prima facie* obviousness requires that three criteria be met: (1) a suggestion or motivation in the cited references or in the art to modify or combine the cited references; (2) the cited references must provide a reasonable expectation of successfully achieving the claimed invention; and (3) the prior art, either alone or combination, must teach or suggest each and every limitation. *In re Vaeck*, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991); *In re* Wilson, 165 U.S.P.Q. 494, 496 (CCPA 1970).

A. The Recited References Do Not Teach or Suggest Each and Every Limitation f Claims 15 and 17-29.

Claims 15 and 17-29 stand rejected under 35 U.S.C. § 103. The Patent Office alleges that the combination of cited references teach the claimed invention since the Y-GG/A motif is present in B-type DNA-polymerases including those taught by Truniger *et al.* (1996 & 1999), Pisani *et al.* (1998) and Geneseq AAW29323, the latter polymerase which is allegedly 99.1% homologous to the polymerase of the instant invention. Office Action mailed January 24, 2003, pages 5-6.

Applicants submit, however, that the Patent Office ignores the differences in polymerase structure outside of the Y-GG/A motif that impart functional effects of mutating the motif's tyrosine residue, as discussed in Applicant's Response mailed November 11, 2002, and below. For this reason, the Patent Office's reliance upon MPEP 2112.01 is misplaced. MPEP 2112.01 discusses case law precedent, for example, *In re Best*, 562 F.2d 1252, 195 U.S.P.Q. 430 (CCPA 1977), that where structure recited in the reference is substantially identical to that of the claims, claimed properties or functions are presumed to be inherent. Nonetheless, evidence showing that the prior art products do not *necessarily* possess the characteristics of the claimed products may be used to rebut the Patent Office's assertion of inherent properties of the prior art polymerases based upon similarity of structure. *See In re Best*, 562 F.2d 1252, 1255, 195 U.S.P.Q. 430, 433 (CCPA 1977); MPEP § 2112.01.

The specification states on page 4, lines 2-5, that the observed effects of mutation on polymerase and exonuclease activities in the ϕ29 and *Sso* polymerases do not completely correspond to the effects obtained for the *Tag* polymerase and thus the effect of the mutations on the performance of the mutants in PCR are not predictable, regardless of whether they are a mutant of Geneseq AAW29323 or the mutant polymerases of Claim 15 or of Claims 17-29 depending from Claim 15. For example, a tyrosine to serine mutation in the Y-GG/A motif of the *Sso* polymerase *lowered* exonuclease activity (Pisani *et al.*, table 2), whereas in the *Tag* polymerase a similar mutation *increased* exonuclease activity (Specification, Figure 1). Thus, the polymerases of the cited references do not *necessarily* possess the characteristics of the claimed products.

The Patent Office contends that nowhere in Claim 15, nor Claims 17-27, is the limitation present that requires the mutant polymerase to be used in PCR. Applicants submit that amended independent Claim 15 recites a mutant polymerase that, *inter alia*, is suitable

for polymerase chain reactions, whereas the ϕ29 and *Sso* polymerases of Pisani *et al.* (1998) and Truniger *et al.* (1996 & 1999) are not suitable for PCR. Geneseq AAW29323 does not teach the mutation as in Claim 15, nor, to Applicant's knowledge, is it known what effects would result from mutation of the tyrosine of the Y-GG/A motif of Geneseq AAW29323. Accordingly, the recited references do not meet the claimed limitations in Claims 15 and 17-29, since each claim either recites a polymerase suitable for PCR or else depends from such a claim.

Additionally, with respect to Claim 19, in response to Applicants' contention that not one of the cited references, Truniger *et al.* (1996 and 1999), Pisani *et al.*, and Geneseq AAW29323 teach a mutant polymerase wherein the wild-type form is SEQ ID NO:34, the Patent Office alleged that since Claim 19 is drawn to a *mutant*, this would embrace a Y-GG/A motif mutant of the Geneseq AAW29323, which contains a five amino acid difference from the polymerase of SEQ ID NO:34. Office Action mailed January 24, 2003, page 6. Amended Claim 19 recites ". . . wherein the difference between the mutant polymerase and the wild-type form consists of the single amino acid substitution of the tyrosine of the Y-GG/A amino acid motif in the wild-type polymerase." The cited references do not teach or suggest each and every limitation of Claim 19 since Geneseq AAW29323 differs from the polymerase of SEQ ID NO:34 in five amino acids other than the tyrosine of the Y-GG/A amino acid motif.

Furthermore, amended Claim 23 recites a mutant polymerase wherein the tyrosine of the Y-GG/A amino acid motif is substituted with an asparagine. Not one of the references of Truniger *et al.* (1996 and 1999), Pisani *et al.*, and Geneseq AAW29323 teach or suggest a mutant polymerase wherein the tyrosine of the Y-GG/A amino acid motif is substituted with an asparagine.

Since, as explained above, the cited references alone or combination do not teach or suggest every limitation of amended Claim 15 or of Claims 17-29 which depend directly or indirectly from Claim 15, Applicants respectfully request that the rejection of Claims 15-29 under 35 U.S.C. § 103(a) be withdrawn.

B. <u>There is No Motivation to Combine References</u>

In the Office Action mailed June 24, 2003, the Patent Office states that "one of ordinary skill in the art would have been motivated to make the [tyrosine to phenylalanine]

mutation for the favorable polymerase results taught by Truniger *et al.* (1996)." Office Action mailed January 24, 2003, page 7.

From the outset, Applicants submit that while independent Claim 15 encompasses a mutant polymerase wherein the tyrosine of the Y-GG/A amino acid motif is substituted with phenylalanine, this is not the case with dependent Claims 22 and 23 which encompass substitutions of the tyrosine of the Y-GG/A amino acid motif to amino acids other than phenylalanine. Therefore, Applicants submit that the favorable results on the polymerase activity of a tyrosine to phenylalanine mutation as shown in the ϕ29 polymerase by Truniger *et al.* would not motivate one of skill to produce a mutant polymerase with tyrosine substituted with an amino acid having a hydrophilic side chain or that is an asparagine residue as in Claims 22 and 23, respectively. Applicants therefore respectfully request that the rejection of Claims 22 and 23 under 35 U.S.C. § 103(a) be withdrawn.

With respect to amended Claim 15, Applicants respectfully submit that the Patent Office is engaging in an improper hindsight reasoning to reconstruct the claimed invention using the Applicant's structure as a template and selecting elements from references to fill the gaps. *See, e.g., Interconnect Planning Corp. v. Feil*, 774 F.2d 1132, 1143, 227 U.S.P.Q. 543, 551 (Fed. Cir. 1985). Truniger *et al.* (1996 and 1999), and Pisani *et al.* teach eighteen different mutant polymerases of wild-type ϕ29 and *Sso* polymerases, but since neither the ϕ29 nor the *Sso* polymerases are suitable for PCR it is unknown which mutations, if any, as shown by Truniger *et al.* (1996 and 1999), and Pisani *et al.* would result in the useful characteristics of a polymerase suitable for PCR.

For example, as discussed in the specification, a mutation, such as the G389A in *Tag* polymerase, displays the opposite effect than the corresponding mutant in ϕ29 DNA polymerase: while G→ A in *Tag* DNA polymerase almost knocks out polymerase activity, in ϕ29 DNA polymerase G→ A mutant this activity is clearly enhanced. Specification, page 4, lines 8-10. This illustrates that the effect of the mutations on the performance of a mutant polymerase in PCR was not predictable.

Furthermore, even though the Y→ F mutation in the ϕ29 and *Sso* polymerases as taught by Truniger *et al.* (1996 and 1999) and Pisani *et al.* represent only two of the eighteen mutants discussed in cited references, the Patent Office focuses exclusively on the results of Y→ F mutation since as it turns out in light of the teachings in the specification, this mutation generally shows increased polymerization, albeit with different magnitudes of effect, in each

of the ϕ29, *Sso*, and *Tag* polymerases. Even so, the Y→ F mutation in the polymerase of Claim 15 was found to have the useful feature of improved PCR performance without a significant change in fidelity as compared to wildtype polymerase. *See* specification, page 7, lines 13-17. Nothing in the cited references discusses the use of the Y→ F mutation for improved PCR performance. Indeed, the Y→ F mutation in the ϕ29 polymerase resulted in significantly decreased exonuclease activity (7% of wildtype ϕ29 polymerase; Truniger *et al.* (1996), page 3433, col. 2) which could just as well lead to an expectation that the Y→ F mutation in the polymerase would have decreased fidelity in PCR performance, whereas the specification describes the exonuclease activity in the Y→ F mutant *Tag* polymerase to be 90% of wildtype polymerase. Specification, Figure 1.

Applicants respectfully submit that despite teaching Y→ F mutants of ϕ29 and *Sso* polymerases, nothing in the Truniger *et al.*, or Pisani *et al.*, points to the Y→ F mutation specifically, out of the various other mutations taught therein, as being particular advantageous for PCR suitability whether in Geneseq AAW29323 or in the mutant polymerase of the invention.

The cited references do not teach mutation of the tyrosine of the polymerase Y-GG/A motif to amino acids recited in Claims 22 and 23. Moreover, Applicants submit that it is only in a retrospective view of the teachings of the instant specification that the Patent Office finds the cited references to teach or suggest the selection and use of the mutation as encompassed in Claim 15, or any claims dependent therefrom. Accordingly, since nothing in the prior art suggests the instant tyrosine mutations for improved PCR performance, as encompassed in Claim 15, and Claims 17-29 dependent from Claim 15, the suggestion or motivation to modify or combine the cited references has not been established. Applicants respectfully request the withdrawal of the rejection of Claims 15 and 17-29 under 35 U.S.C. § 103(a).

C. <u>There Is No Reasonable Expectation of Success</u>

Previously, Applicants submitted that there was no reasonable expectation of success since (1) the effects of mutating the tyrosine residue with the Y-GG/A motif do not completely correspond to the effects obtained for the *Tag* polymerase, and (2) the effects of mutating said tyrosine residue is not predictable in terms of PCR performance since neither the ϕ29 and *Sso* polymerases are suitable for PCR. Amendment and Response mailed November 11, 2002, pages 8-9. In response, the Patent Office stated that Applicants were arguing limitations not found in the claims, as PCR is only one type of amplification reaction. Office Action mailed January 24, 2003 page 9.

Claim 15, as amended, recites a polymerase suitable for PCR, and such recited element is likewise applicable to Claims 17-29 depending from Claim 15. Hence, Applicants respectfully submit that there was no reasonable expectation of success for the reasons stated in the Amendment and Response mailed November 11, 2002, pages 8-9. Accordingly, Applicants respectfully request the rejection of Claims 15 and 17-29 be withdrawn.

D. Applicants' Invention Shows Surprising Results

For reasons discussed above, the Examiner has not established a *prima facie* case of obviousness under 35 U.S.C. § 103(a) against Claims 15, and 17-29. But even assuming, *arguendo*, that the cited references could establish a *prima facie* case, it is overcome by the unexpected results achieved by the inventors. *See, e.g., In re Soni*, 54 F.3d 746, 34 U.S.P.Q.2d 1684, 1687 (Fed. Cir. 1995). Mutants as encompassed in Claim 15 show substantial differences in the characteristics measured, relative to the *Sso* and ϕ29 polymerases, or what could have been predicted from Pisani *et al.*, Truniger *et al.* (1996), and Truniger *et al.* (1999), for reasons explained in the Amendment and Response mailed November 11, 2002, pages 10-11 (comparing results of mutations in *Tag* to mutations in the *Sso* and ϕ29 polymerases).

However, the Patent Office first states that Applicant argues limitations not found in the claims since the claims do not specifically claim a *Tag* polymerase, but rather a mutant having 80% homology to instant SEQ ID NO:34, one kind of polymerase from the organism *Thermococcus aggregans*. Office Action mailed January 24, 2003. Applicants respectfully submit that an exemplary showing of unexpected results for *Tag* polymerase is sufficient to rebut a *prima facie* case of obviousness where *Tag* polymerase is encompassed in the mutant polymerase of Claim 15 having 80% homology to instant SEQ ID NO:34 and wherein the mutant polymerase suitable for PCR, since one of skill could clearly ascertain a trend in the exemplified data to any other mutant polymerase falling within the scope of Claim 15. *See In re Kollman*, 201 U.S.P.Q. 193, 199 (CCPA 1970) ("unobviousness of a broader claimed range can, in certain instances, be proven by a narrower range of data"); MPEP 2144.08, p. 2100-144.

The Patent Office next states that "there would have been an expectation of success in the art that a Y→ F mutation would have a positive effect on polymerase activity of the sequence taught in Geneseq AAW29323 . . . ." Further, the Patent Office states that it is not clear why applicant points to the difference in exonuclease activity as between the mutant polymerases taught by Pisani *et al.*, Truniger *et al.*, and the instant invention, since

polymerase activity is what is needed and exonuclease activity values do not adversely effect the polymerase activities. Office Action of January 24, 2003, page 10.

Claim 15, as amended, encompasses a mutant polymerase suitable for PCR. As the specification teaches, the quotient of error rates of a polymerase in PCR is dependent on the combination of polymerase and exonuclease activities. Specification, page 7, lines 1-18 and Fig. 5 (showing all tyrosine mutants had similar or better quotient of error rates than wild-type *Tag* polymerase). Thus, exonuclease activity is important to polymerase suitability for PCR. Even if one ignores the unsuitability of the mutant *Sso* and ϕ29 polymerases for PCR generally, one cannot ignore the lower exonuclease activities shown by the mutant *Sso* and ϕ29 polymerases to focus solely on the polymerase activities in comparison to the *Tag* polymerase. Applicants respectfully submit that lower exonuclease activities of the mutant *Sso* and ϕ29 polymerases suggest that the mutants are not suitable for PCR. For these reasons, Applicants respectfully disagree with the Patent Office's position that no surprising results have been demonstrated.

In summary, there is no suggestion or motivation, either in the cited references or in the art, to modify or combine the cited references, nor is there a reasonable expectation of success of claimed subject matter. But even assuming, *arguendo*, that were a *prima facie* case of obviousness established, the data presented in the instant application exhibit surprising and unexpected results to a person of ordinary skill in the relevant art. Applicants respectfully request the withdrawal of the rejections of Claims 15-29 under 35 U.S.C. § 103(a).

E. <u>New Claims 30-32 Are Patentable Over the Cited References</u>

Applicants submit that new Claims 30-32 are not obvious over Geneseq AAW29323 (the sequence in Frey et al., DE 196 11 759 A1) in view of Pisani *et al.* (1998), and Truniger *et al.* (1996 & 1999). First, each of Claims 30, 31 and 32 depend from Claim 15, and the mutant polymerase of Claim 15 is patentable over the cited references as explained above. Second, Claim 30 recites a mutant polymerase wherein the tyrosine of the Y-GG/A amino acid motif is substituted with a tryptophan or histidine, and not one of the cited references teaches or suggests a tryptophan or histidine residue in the Y-GG/A motif in their polymerases.

Next, Claim 31 recites a mutant polymerase wherein the tyrosine of the Y-GG/A amino acid motif is substituted with a serine. While Pisani *et al.* (1998), and Truniger *et al.*

(1996 & 1999) teach a tyrosine to serine mutation in the *Sso* and ϕ29 polymerases, respectively, the demonstrable different effects of the analogous Y→ S mutations in each of the two polymerases evidence that one of skill in the art could hardly have known or expected a similar substitution of tyrosine to serine would result in a useful polymerase for PCR, whether it be Geneseq AAW29323 or the mutant polymerase of Claim 31. For example, the Y→ S mutation in the *Sso* polymerase resulted in a reduction of polymerase activity (6% of *Sso* wildtype) and a *decrease* in exonuclease activity (5% of wildtype). Pisani *et al.*, page 1501, tbl. 2. On the other hand, the Y→ S mutation in the ϕ29 polymerase resulted in little or no polymerase activity and had 380% of the exonuclease activity as compared to ϕ29 wildtype. Truniger *et al.* (1996), page 3433, tbl. 1. By comparison, the Y387S mutation in *Tag* resulted in a mutant with 17.8% of the wildtype *Tag* polymerase activity and 187% of the wildtype exonuclease activity. Specification, Fig. 1. Therefore, Applicants submit that Claim 31 is not obvious over the cited references.

Finally, Claim 32 recites a polymerase chain reaction process using the mutant polymerase of Claim 15. Applicants submit that neither Pisani *et al.* (1998), nor Truniger *et al.* (1996 & 1999), nor Geneseq AAW29323 taken alone or combination teach or suggest use of the mutant polymerase of Claim 15 for a process of PCR or for that matter any polymerase suitable for use in PCR.

CONCLUSION

Applicants submit that Claims 15 and 17-32 satisfy all of the criteria for patentability and are in condition for allowance. An early indication of the same and passage of Claims 15 and 17-32 to issuance is therefore kindly solicited.

No fees other than those required for the extension of time and the notice of appeal are believed due in connection with this response. However, the Commissioner is authorized to charge all required fees, fees under 37 C.F.R. § 1.17, or credit any overpayment, to Pennie & Edmonds LLP U.S. Deposit Account No. 16-1150.

Respectfully submitted,

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